REMARKS

Claims 1-27 are pending in the present application. Claims 18-27 have been withdrawn from consideration. By virtue of this response, claims 1-10 and 15 have been amended; and claims 11-14, 16, and 17 have been canceled. Accordingly, claims 1-10 and 15 are currently under consideration. Support for amendment of claim 1 is found in the specification, *inter alia*, on page 3, lines 11-15; and page 22, lines 6-8. Support for amendment of claim 10 is found in the specification, *inter alia*, on page 13, lines 9-27.

Applicants respectfully note that claim 7 is not withdrawn from consideration. In the response to the Restriction Requirement, Applicants made species election to RL-65 and claim 7 reads on this species. Thus, claim 7 is not withdrawn from consideration.

With respect to all claim amendments and cancellations, Applicants have not dedicated or abandoned any unclaimed subject matter and moreover have not acquiesced to any rejections and/or objections made by the Patent Office. Applicants reserve the right to pursue prosecution of any presently excluded claim embodiments in future continuation and/or divisional application. .

Information Disclosure Statement

The Examiner has acknowledged that the Information Disclosure statement filed on Dec. 12, 2003 has been received. However, the Examiner states that since the non-patent literature references are not found in the parent applications, IDS references 7-36 and 38-46 have not been considered.

Applicants respectfully note that copies of these references were submitted in an Information Disclosure Statement and/or Office Action directed to the related applications Serial Numbers 09/218,539 and 09/614,483, and the submission complies with 37 C.F.R. §1.98(a)-(c). Accordingly, Applicants are not required to provide copies of these references under 37 C.F.R. §1.98(d) and MPEP 609(A)(2). For Examiner's convenience, copies of these references are attached

with this amendment. Applicants would appreciate the Examiner initialing and returning the form PTO-1449, indicating that these references have been considered and made of record herein.

Applicants also note that a Supplemental Information Disclosure Statement is submitted with this amendment. Applicants would appreciate the Examiner initialing and returning the Form PTO/SB/08a/b, indicating that the information has been considered and made of record herein.

Specification

The Examiner states that "Table II" is missing from the specification of the instant application. Applicants note that Table I and Table II were in the specification of the parent applications, U.S. Ser. No. 09/218,539 and 09/614,483; and these two tables were omitted in the copying for filing of the present application. MPEP 608.01(p)IB provides that applicant may include a statement at the time of filing a later application incorporating by reference the prior application from which priority is claimed, and the inclusion of such an incorporation by reference statement in the later-filed application will permit applicant to include subject matter from the prior application into the later-filed application without the subject matter being considered as new matter. Applicants note that the present application was filed with the incorporation by reference statement recited on page 1 of the present application. Accordingly, Applicants have amended the specification of the present application to incorporate Table I and Table II from the parent applications. In view of the support for these tables in the parent applications, Applicants respectfully submit that the present amendments introduce no new matter to the instant application.

The Examiner also states that the description of Figure 9 on page 32 of the instant application does not match with Figure 9. Applicants acknowledge that Figure 9 in the instant application does not match with the description. However, Applicants respectfully note that the results are described in the specification on page 32, lines 3-13.

In view of the above, Applicants respectfully request that the objection be withdrawn.

Rejections under 35 U.S.C. §112, second paragraph

Claims 1-6 and 8-17 are rejected under 35 U.C.S. §112, second paragraph, as allegedly being ambiguous in the recitation of "the cell". The Examiner states that the base claim 1 contains more than one type of cells.

Without acquiescing to the rejection, Applicants respectfully note that claim 1 has been amended, and accordingly, the term "the cells" in claims 2-10 and 15 is clear. Applicants respectfully request the rejection be withdrawn.

Claim 17 is rejected under 35 U.C.S. §112, second paragraph, as allegedly being indefinite for reciting "functional effect". The Examiner alleges that the metes and bounds of this functional effect are unclear and ambiguous.

Applicants respectfully note that claim 17 is canceled. Thus, this rejection is moot. Applicants respectfully request that the rejection be withdrawn.

Claim 10 is rejected under 35 U.C.S. §112, second paragraph, as allegedly being indefinite in the recitation of ASC, ESC, ROG, BUD, NODD, BR516, RL-65, and NEP. The Examiner states that these terms are merely laboratory designations which do not clearly define the claimed product since different laboratories may use the same laboratory designations to define completely distinct cell lines.

Applicants respectfully note that claim 10 is amended to incorporate some of the characteristics and the full names for the cells referred to as ASC, ESC, ROG, BUD, NODD, BR516, RL-65, and NEP. As discussed below, Applicants assure that acceptable deposits will be made for these cells on or before the payment of the issue fee of the present application. Thus, Applicants respectfully request that the rejection be withdrawn.

In view of the above, Applicants respectfully request that rejections under 35 U.C.S. §112, second paragraph be withdrawn.

Rejections under 35 U.S.C. §112, first paragraph

Claim 10 is rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which is not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Specifically, the Examiner states that the instant specification does not disclose a repeatable process to obtain the cell lines recited in claim 10, ASC, ESC, ROG, BUD, RED, NODD, BR516, RL-65 and NEP, and it is not apparent if the cell lines are readily available to the public.

MPEP 2406 provides that a necessary deposit need not be made by an applicant until the application is in condition for allowance so long as the applicant provides a written assurance that an acceptable deposit will be made on or before the payment of the issue fee, and this written assurance must provide sufficiently detailed information to convince the examiner that there is no outstanding issue regarding deposits that needs to be resolved. Accordingly, Applicants respectfully request that the rejection be withdrawn. Without acquiescence to the rejection, Applicants submit herewith the Written Assurance by Jennie P. Mather, which assures that acceptable deposits for the cell lines recited in claim 10 will be made on or before the payment of the issue fee for the present application. Applicants respectfully submit that in view of the Written Assurance, claim 10 satisfies the requirement under 35 U.S.C. §112, first paragraph once the deposits are made.

Rejections under 35 U.S.C. §103(a)

A. Claims 1-6, 8-11, 13-17 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Okabe et al. (Cancer Res., 1984, 44:5273-5278) in view of Mather et al. (U.S. Pat. No. 5,364,785). The Examiner states that Okabe et al. teach a method for producing monoclonal antibodies that bind to antigens that are heterologous to a host mammal, and Okabe et al. further teach that the antigen is on the surface membrane and the origin of the cells are embryonic and endodermic. The Examiner further states that the claimed invention differs from Okabe et al. teachings by using the intact cells (RL-65) grown in the serum free media, morphology of cells and biological substrate. The Examiner further states that Mather et al. teach a method of isolating an epithelial lung cell line (RL-65) in the serum free media. The Examiner concludes that

it would have been obvious to one of the ordinary skill in the art at the time the invention was made to employ an isolated epithelial cell line RL-65 taught by Mather et al. in the monoclonal antibody generation method taught by Okabe et al.

Without acquiescence to the rejection, Applicants respectfully note that claim 1 has been amended to recite "the cells are introduced into the mammal without adjuvant". Applicants respectfully submit that claims as amended are not obvious over Okabe et al. in view of Mather et al.

Applicants respectfully submit that the cited references, when combined, do not teach or suggest all the claim limitations. Okabe et al. do not disclose whether or not an adjuvant was used for immunizing mice with the cells. See page 5273, right column, second paragraph under "MATERIALS AND METHODS". Okabe et al. disclose that tumor cells that were grown in 5% fetal bovine serum and maintained in BALB/c nude mice were used for immunization to generate antibodies.

Applicants submit herewith a declaration of Jennie P. Mather pursuant to 37 C.F.R. §1.132 (hereafter "Mather Declaration"). As set forth in paragraph 12 and 13 of the Mather Declaration, the skilled artisan routinely used Freund's adjuvant before the priority date of the present invention. Exhibit 1 of the Mather Declaration shows a protocol for immunizing mice in order to generate monoclonal antibodies, taken from the standard treatise Current Protocols in Immunology. As stated in the Mather Declaration, immunization of a host mammal with viable cells in the absence of adjuvant was not common general knowledge before the priority date of the instant application. Accordingly, the lack of experimental details in Okabe et al., and the conventional use of Freund's adjuvant at the time the reference was published would have led the ordinary skilled artisan to conclude that the authors used Freund's adjuvant in the preparation of their monoclonal antibodies.

Mather et al. do not teach or suggest the claimed invention. Mather et al. disclose methods of isolating and culturing lung cell lines from a heterogeneous population of lung cells.

Mather et al. do not teach or suggest introducing the cells into a host mammal for immunization to produce a population of monoclonal antibodies that bind to antigens representative of the specific cell type. Mather et al. do not disclose methods of immunization without adjuvant.

Accordingly, the references cited by Examiner, even if combined, do not teach or suggest all the claim limitations.

In addition, Applicants respectfully submit the references cited by the Examiner do not provide a reasonably expectation of success. As discussed above, the references do not teach or suggest that introducing into a host mammal a plurality of viable and intact cells without adjuvant would generate a population of monoclonal antibodies that bind to antigens representative of a specific cell type, wherein the surface of the cells are free of serum. As stated in the Mather Declaration, at the time of the present invention, the standard practice uses Freunds adjuvant with an immunogen to boost host animal's immune response to the immunogen. However, one key feature of the present invention for generating a population of monoclonal antibodies that specifically bind to antigens representative of a particular type involves preparing the immunogen without the use of adjuvant. Thus, one skilled in the art would not have a reasonable expectation of success for generating a population of monoclonal antibodies that bind to antigens representative of a specific cell type without use of the adjuvant.

Using the methods taught in the instant application, the inventors generated a population of monoclonal antibodies reactive with antigens representative of embryonic pancreatic ductal cells. Thirteen out of fifteen of the different monoclonal antibodies examined recognized distinct antigens on the cell surfaces. See, e.g., page 18, lines 23-31 of the specification. Of the thirteen monoclonal antibodies, two exemplary monoclonal antibodies and their selectivity for staining certain body tissues, sub-tissue structures, and particular layers of cells within a tissue are described in detail in the Examples. As stated in the Mather Declaration, prior to the present invention, the pools of monoclonal antibodies generated by practice of the commonly known methods were not necessarily or predictably directed against the cell surface antigens of the cells of interest, or if they were, it was not predictably that they would recognize the antigens in their native conformation. The Mather

Declaration also states that the populations of antibodies generated prior to this invention were not likely to be predictably directed against the antigens representative of a particular cell surface, or representative of those appearing on a particular tissue (or sub-tissue) type. Thus, as stated in the Mather Declaration, the invention described in the present application satisfies the needs for methods for generating a population of monoclonal antibodies that specifically binds to antigens representative of a particular cell type, and the results of the practice of the present invention are unexpected.

In view of the above, Applicants respectfully submit that claims as amended are not obvious over Okabe et al. in view of Mather et al., and request withdrawal of this rejection.

B. Claims 1 and 12 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Okabe et al. (Cancer Res., 1984, 44:5273-5278) in view of Mather et al. (U.S. Pat. No. 5,364,785) and Sharp et al. (U.S. Pat. No. 4,487,829). The Examiner states that the claimed invention differs from teachings of Okabe et al. and Mather et al. by using ELISA for selection. The Examiner further states that Sharp et al. teach using ELISA assay as a diagnostic and therapeutic tool due to specific reactivity of monoclonal antibody to antigenic determinants. The Examiner concludes that it would have been obvious to one of the ordinary skill in the art at the time the invention was made to employ an ELISA taught by Sharp et al. as a selecting tool in the monoclonal antibodies generated by a method taught by Okabe et al. and Mather et al.

Applicants note that claim 1 has been amended to recite "the cells are introduced into the mammal without adjuvant", and claim 12 has been canceled. Applicants respectfully submit that claim 1 as amended is not obvious over Okabe et al. in view of Mather et al. and Sharp et al.

Applicants respectfully submit that the cited references, when combined, do not teach or suggest all the claim limitations. As discussed above, neither Okabe et al. nor Mather et al. teach or suggest methods of immunizing a host mammal to produce a population of monoclonal antibodies that bind the antigens representative of a specific cell type that are heterologous to a host mammal by introducing into the host mammal a plurality of viable and intact cells of said cell type, wherein

the surface of the cells are free of serum and the cells are introduced into the mammal without adjuvant. Sharp et al. do not cure this deficiency. Sharp et al. do not teach or suggest methods of immunization without adjuvant. Sharp et al. disclose methods of generating monoclonal antibodies against adenoviruses by immunizing mice with native virions irradiated with UV or extracts of infected cells. Sharp et al. also teach immunizing with Freund's adjuvant (complete Freund's for the primary injection and incomplete Freund's for the boosts). See, col. 3, lines 3-6. Thus, the references cited by the Examiner, even if combined, do not teach or suggest all the claim limitations of claim 1 as amended.

Applicants respectfully submit that the cited references do not provide the motivation to combine reference teachings. As discussed above, Okabe et al. and Mather et al. do not provide any teaching or suggestion of methods of immunizing a host mammal to produce a population of monoclonal antibodies that bind the antigens representative of a specific cell type that are heterologous to a host mammal by introducing into the host mammal a plurality of viable and intact cells of said cell type, wherein the surface of the cells are free of serum and the cells are introduced into the mammal without adjuvant. Sharp et al. do not teach or suggest immunization methods comprising introducing a plurality of viable and intact cells, wherein the surface of the cells are free of serum and the cells are introduced into the mammal without adjuvant. Sharp et al. disclose methods of generating monoclonal antibodies against adenovirus by introducing virions or extracts of infected cells. Thus, Sharp et al. do not provide any additional motivation to combine the reference teachings.

In addition, since none of Okabe et al., Mather et al., and Sharp et al. provides any teaching or suggestion of methods of immunizing a host mammal to produce a population of monoclonal antibodies that bind the antigens representative of a specific cell type that are heterologous to a host mammal by introducing into the host mammal a plurality of viable and intact cells of said cell type, wherein the surface of the cells are free of serum and the cells are introduced into the mammal without adjuvant, it would not have been obvious for one of ordinary skill in the art to combine the teachings of these references with a reasonably expectation of success.

In view of the above, Applicants respectfully submit claim 1 as amended is not obvious over Okabe et al. in view of Mather et al. and Sharp et al. Applicants respectfully request that the rejection be withdrawn.

CONCLUSION

In view of the above, each of the presently pending claims in this application is believed to be in immediate condition for allowance. Accordingly, the Examiner is respectfully requested to withdraw the outstanding rejection of the claims and to pass this application to issue. If it is determined that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number given below.

In the event the U.S. Patent and Trademark office determines that an extension and/or other relief is required, applicant petitions for any required relief including extensions of time and authorizes the Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to Deposit Account No. 03-1952 referencing docket no.*. However, the Commissioner is not authorized to charge the cost of the issue fee to the Deposit Account.

Dated: Sept. 26, 2005

Respectfully submitted,

By _____

Jie Zhou
Registration No.: 52,395
MORRISON & FOERSTER LLP
755 Page Mill Road
Palo Alto, California 94304-1018
(650) 813-5922